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Randomized, Controlled Trial of a 13-Valent Pneumococcal Conjugate Vaccine Administered Concomitantly with an Influenza Vaccine in Healthy Adults

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A randomized, double-blind, phase 3 trial evaluated the immunogenicity, safety, and tolerability of a 13-valent pneumococcal conjugate vaccine (PCV13) coadministered with trivalent inactivated influenza vaccine (TIV) in pneumococcal vaccine-naive adults. Participants ages 50 to 59 years ($n = 1{,}116$) received TIV with PCV13 (group 1) or placebo (group 2) (1:1 randomization); 1 month later, group 1 received placebo and group 2 received PCV13. A hemagglutination inhibition (HAI) assay for TIV and a standardized enzyme-linked immunosorbent assay for pneumococcal serotype-specific immunoglobulin G (IgG) were performed and opsonophagocytic activity (OPA) titers (assessed *post hoc*) were measured at baseline and 1 and 2 months postvaccination. The rises in HAI assay geometric mean titer (GMT) and percentage of participants in groups 1 and 2 with ≥4-fold increases in HAI responses (A/H1N1, 84.0% and 81.2%, respectively; A/H3N2, 71.1% and 69.5%, respectively; and B, 60.6% and 60.3%, respectively) were similar. In group 1, all serotypes met the predefined IgG geometric mean concentration (GMC) ratio noninferiority criterion relative to group 2, but GMCs were lower in group 1 than group 2. When comparing group 1 with group 2, 5 serotypes did not meet the OPA GMT ratio noninferiority criterion, and OPA GMTs were significantly lower for 10 serotypes. PCV13 injection site reactions were similar and mostly mild in both groups. Systemic events were more frequent in group 1 (86.2%) than group 2 (76.7%; $P < 0.001$); no vaccine-related serious adverse events occurred. Coadministration of PCV13 and TIV was well tolerated but associated with lower PCV13 antibody responses and is of unknown clinical significance. Given the positive immunologic attributes of PCV13, concomitant administration with TIV should be dictated by clinical circumstances.

Diseases caused by *Streptococcus pneumoniae* are a major health problem worldwide in children and adults, with an estimated 1.6 million people dying each year from the infection (30). Children in the first few years of life and adults ≥50 years of age are at an increased risk of developing invasive pneumococcal disease (IPD) (11). Pneumococcal infections are becoming more difficult to treat due to the increased prevalence of antimicrobial resistance; therefore, vaccination has become an important preventive strategy (4, 30).

Children aged <2 years have an immature immune system and respond poorly to polysaccharide vaccines that elicit predominantly T-cell-independent immune responses (18). The immunogenicity of these formulations has been improved by conjugating the purified capsular saccharides of *S. pneumoniae* to an immunogenic protein carrier, which overcomes the limitations of unconjugated pneumococcal polysaccharide vaccines (PPVs) in young children by eliciting a T-cell-dependent response with robust immunological memory (18). A pneumococcal conjugate vaccine (PCV) containing *S. pneumoniae* serotypes, which is highly effective in preventing IPD in infants and young children, is available (2, 19, 23). The 7-valent PCV (PCV7) (Prevnar/Prevenar; Pfizer, Pearl River, NY) contains *S. pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F and has been in routine use since the year 2000 (31).

The emergence of serotypes not present in PCV7, particularly serotypes 3, 7F, 15, 33, and 19A (26), led to the development of a 13-valent PCV (PCV13). This new vaccine, which includes serotypes 1, 3, 5, 6A, 7F, and 19A in addition to those in PCV7, was recently approved in Europe and the United States for the prevention of IPD and otitis media in children from age 6 weeks up to their sixth birthday (31) and later for use in adults aged ≥50 years. Additionally, the Advisory Committee on Immunization Practices recommends a single dose of PCV13 for children aged 6 to 18 years who have not previously received PCV13 and who are at increased risk for IPD because of anatomic or functional asplenia, including sickle cell disease, immunocompromising conditions such as HIV infection, cochlear implant, or cerebrospinal fluid leaks, regardless of whether they have previously received PCV7 or 23-valent PPV (PPV23) (17). As with PCV7, each of the 13 polysaccharides in PCV13 is covalently conjugated to a common carrier protein, diphtheria toxin cross-reactive material 197 (CRM197).

The currently recommended PPV23 covers approximately 90% of *S. pneumoniae* serotypes that cause IPD in older adults. However, the vaccine has the drawbacks of poorly defined vaccine efficacy (particularly against pneumococcal pneumonia in older adults), lack of establishment of T-cell memory, and a decline of

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antibodies over 5 years at different rates for the 23 serotypes (27). However, some studies have demonstrated that subjects who were revaccinated with PPV23 5 years after the initial dose of PPV23 had antibody levels that were comparable to those after the initial dose for selected serotypes (13, 16). In contrast, the conjugate vaccines may induce quantitatively, and possibly qualitatively, improved immune responses in adults compared with the polysaccharide vaccines. Studies indicate that PCVs (including PCV13) are safe and immunogenic in adults and induce immunologic memory, boost antibody response, and improve protection against pneumococcal disease in this population (8, 21, 22).

The present study was conducted to evaluate the immunogenicity, safety, and tolerability of PCV13 when administered concomitantly with the trivalent inactivated influenza vaccine (TIV) in adults aged 50 to 59 years who had not previously received a pneumococcal vaccine. The study was performed as part of an ongoing program to develop PCV13 for use in adults.

MATERIALS AND METHODS

Design overview. This phase 3, parallel-group, randomized, double-blind, multicenter trial was conducted at 34 sites in the United States from September 2007 to November 2008. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki, and written informed consent was obtained from all participants prior to enrollment.

Participants. Eligible participants included healthy men and women aged 50 to 59 years at the time of enrollment. Adults with underlying diseases that were stable for 6 or more weeks prior to vaccination were included. Participants were excluded if they had a history of *S. pneumoniae* infection within the last 5 years, were previously vaccinated with any pneumococcal vaccine or with an influenza- or diphtheria-containing vaccine within the previous 6 months, had a history of any severe adverse reaction associated with a vaccine, had received blood products or gamma globulins within the previous 6 months, had known or suspected immune deficiency or suppression, or had a serious chronic disorder (including metastatic malignancy and severe chronic obstructive pulmonary disease) requiring supplemental oxygen, end-stage renal disease with or without dialysis, clinically unstable cardiac disease, or any other disorder considered by the investigator to preclude participation in the trial.

Interventions. All eligible participants received a dose of TIV during the first study visit and were randomized in a 1:1 ratio to receive a dose of either PCV13 (group 1) or placebo (group 2). One month later, participants in group 1 received the placebo while those in group 2 received a dose of PCV13. Vaccinations (0.5-ml dose) were given intramuscularly into the left (PCV13 or placebo) and right (TIV) deltoid muscles. Blood samples were collected prior to the first vaccination and 1 month after each vaccination.

Vaccines administered. PCV13 contains saccharides from pneumococcal serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F individually conjugated to nontoxic diphtheria toxoid CRM197. The vaccine is formulated to contain 4.4 μg of 6B and 2.2 μg of each of the other 12 saccharides. Each 0.5-ml dose is formulated with 5.0 mM succinate buffer, pH 5.8, 0.85% sodium chloride, and 0.02% polysorbate 80 and contains 0.125 mg aluminum as aluminum phosphate.

The placebo was formulated similarly but without the CRM197-conjugated pneumococcal saccharides. PCV13 and placebo were filled in identical containers, so that the appearance of the placebo matched that of PCV13.

All participants received the 2007-2008 preparation of the seasonal influenza vaccine (Fluarix; GlaxoSmithKline Biologicals, Rixensart, Belgium), which contained 15 μg each of A/Solomon Islands/3/2006 (H1N1), A/Wisconsin/67/2005 (H3N2), and B/Malaysia/2506/2004.

Study objectives. This study was designed to evaluate the quality of the anti-TIV immune response in participants who received the concomitant administration of PCV13 and TIV (group 1) compared with participants who received TIV alone (group 2). Additionally, the study evaluated whether the immune responses to PCV13 in group 1 are noninferior to those in group 2. This study also evaluated the acceptability of the safety profile of coadministration of PCV13 and TIV in group 1 compared with administration of PCV13 1 month after placebo and TIV in group 2.

Immunogenicity assessments. The immune responses to the three antigens in TIV were compared between group 1 and group 2 at 1 month after administration of TIV using a standard hemagglutination inhibition (HAI) assay. The immunogenicity of PCV13 in groups 1 and 2 was measured using a standardized enzyme-linked immunosorbent assay (ELISA) for serotype-specific immunoglobulin G (IgG) 1 month after PCV13 vaccination (29).

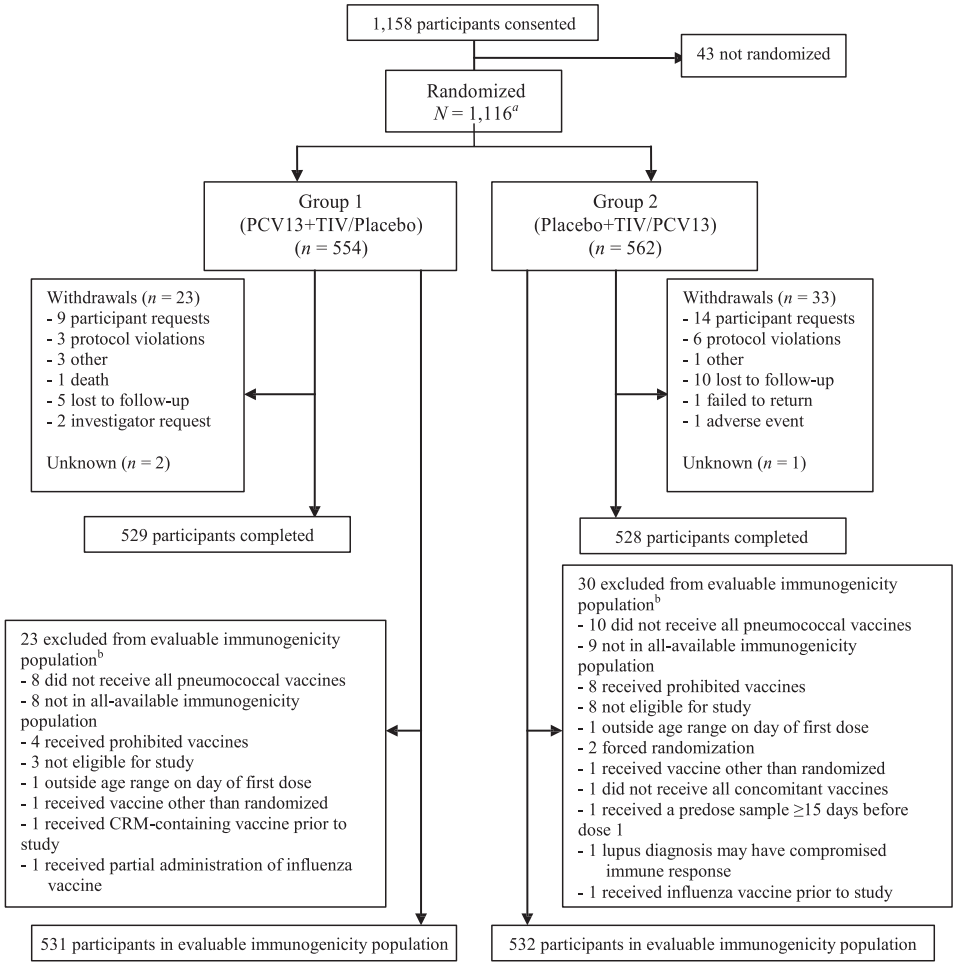
In a *post hoc* analysis, the functional anticapsular opsonophagocytic antibodies were measured with 13 serotype-specific, validated opsonophagocytic activity (OPA) assays (7, 12) in order to further assess antibody responses. Results were summarized using geometric mean titers (GMTs) for each serotype as well as the percentage of participants achieving OPA titers greater than or equal to the lower limit of quantitation (LLOQ). Participants who were included in the IgG subset who had sufficient sera available were included for OPA testing. If subjects in the IgG subset did not have sufficient sera, then additional subjects were selected consecutively from a randomly ordered subject list.

OPA titers were defined as the interpolated reciprocal serum dilution that resulted in complement-mediated killing of 50% of the assay bacteria. The lowest titer that can be determined in the assay (limit of detection [LOD]), regardless of serotype, is 8. However, to quantify functional antibodies with appropriate precision and accuracy, the LLOQ was determined for each serotype-specific OPA assay during assay validation. Titers below the LLOQ were set to a value of 4 (half of the LOD).

The serotype-specific OPA assays do not use an external reference standard; therefore, OPA titers cannot be compared across serotypes. To quantify functional antibodies in the OPA assays with appropriate precision and accuracy, the lower limit of quantitation (LLOQ) was determined for each serotype-specific OPA assay during assay validation. The LLOQ for each serotype-specific OPA assay was used as a cutoff to determine serum response for the immunogenicity population. The stringent qualification and validation approach used for the microcolony OPA (mcOPA) assays did not support a universal LLOQ of 1:8, used to support the pediatric indication for PCV13, for the quantitation of a serum response; thus, the following cutoffs (LLOQs) were used for the mcOPA assays: serotype 1, 1:18; serotype 3, 1:12; serotype 4, 1:21; serotype 5, 1:29; serotype 6A, 1:37; serotype 6B, 1:43; serotype 7F, 1:210; serotype 9V, 1:345; serotype l4, 1:35; serotype 18, 1:31; serotype 19A, 1:18; serotype 19F, 1:48; and serotype 23F, 1:13. Given the range of LLOQs (12 to 345), the individual LLOQs are used for each of the serotypes as serotype-specific cutoffs rather than the previously proposed cutoff of 1:8.

The primary immunogenicity analyses were based on the evaluable immunogenicity population. The evaluable immunogenicity population included all participants who met the eligibility criteria, those randomly assigned to a vaccine group, those receiving all vaccinations in the sequence to which they were assigned, those who had ≥1 valid and determinate assay result for antibody response to any pneumococcal serotype or concomitant vaccine (TIV) antigen, those who had a prevaccination or postvaccination blood sample taken within the prescribed time window, those who received no prohibited vaccinations, and those who had no other major protocol violations.

Safety assessments. The safety profile of PCV13 coadministered with TIV was compared with that of placebo coadministered with TIV followed 1 month later by PCV13. Local reactions (redness, swelling, pain, and limitation of arm movement) at the injection site of PCV13 and placebo were collected for 14 days using an electronic diary completed by the participants. Systemic events, including fever (oral temperature of ≥38°C or 100.4°F), chills, fatigue, headache, vomiting, decreased appetite, rash, new generalized muscle pain, aggravated generalized muscle



[a] Includes 1 participant who was randomly assigned but did not provide informed consent. This participant was not vaccinated and no blood sample was taken, and was withdrawn for "other" reason.
[b] Some participants were excluded for more than 1 reason.

FIG 1 Participant disposition.

pain, new generalized joint pain, aggravated generalized joint pain, and use of antipyretic and pain medications to treat symptoms, were also recorded by the participants. Adverse events were recorded throughout the study period. The safety population included all participants who received at least 1 dose of the study vaccine.

Sample size. Sample size estimation was based on the proportion of seroconverters (at least a 4-fold increase in the titer as assessed by the HAI assay) in each group for TIV comparisons and the geometric mean concentrations (GMCs) in each group for PCV13 comparisons. Sample sizes were computed using NQUERY Advisor version 6.0 (Statistical Solutions Ltd., Cork, Ireland). This study was powered to evaluate noninferiority of antibody responses to PCV13 coadministered with TIV relative to TIV and PCV13 administered separately. For TIV comparisons, sample size calculations assumed a power of 80%, a noninferiority criterion of −0.10 for the difference in proportions of responders, no difference in true responses between groups 1 and 2, a two-sided, type I error rate of 0.05, and a dropout rate of ≤7%. With these assumptions, 511 evaluable participants per group were needed for TIV comparisons. A total of 1,100 participants were required to be randomly assigned to ensure 1,022 evaluable participants for TIV comparisons.

For anti-pneumococcal IgG comparisons, sample size calculations assumed a power of 90%, a 2-fold noninferiority criterion for GMCs, no difference in true responses between study groups, a two-sided, type I error of 0.05, and a dropout rate of ≤7%. On the basis of these assumptions, 281 evaluable participants per group were needed for pneumococcal comparisons.

Randomization. Eligible participants were randomly assigned in a 1:1 ratio to receive PCV13 coadministered with TIV followed 1 month later by placebo (group 1) or placebo coadministered with TIV followed 1 month later by PCV13 (group 2). All participants, study staff, and those assessing the outcomes were blinded to the group assignment.

Statistical analysis. For TIV antigens (A/H1N1, A/H3N2, and B), seroconversion (responder) was defined as a ≥4-fold increase in HAI assay titers from prevaccination to 1 month postvaccination. Exact, two-sided 95% confidence intervals (95% CIs), based on the Chan and Zhang (5) procedure, were computed on the difference in proportions of seroconverters for TIV between group 1 and group 2 at 1 month after the first dose. Noninferiority was declared if the lower limit of the two-sided 95% CI for the difference in proportions of responders (i.e., ≥4-fold increase in HAI assay titers) between groups 1 and 2 was greater than −0.10.

For PCV13, IgG concentrations for each pneumococcal serotype in the vaccine were logarithmically transformed for analysis, and GMCs

TABLE 1 Demographic characteristics of the safety population

Variable	Result[a]		
	Group 1 (PCV13 plus TIV; placebo) (n = 551)	Group 2 (placebo plus TIV; PCV13) (n = 560)	Total (n = 1,111)
Sex, n (%)			
Women	319 (57.9)	322 (57.5)	641 (57.7)
Men	232 (42.1)	238 (42.5)	470 (42.3)
Race, n (%)			
White	502 (91.1)	511 (91.3)	1,013 (91.2)
Black	34 (6.2)	42 (7.5)	76 (6.8)
Asian	5 (0.9)	2 (0.4)	7 (0.6)
Other	10 (1.8)	5 (0.9)	15 (1.4)
Mean age at vaccination, yr (SD)	54.6 (2.8)	54.6 (2.9)	54.6 (2.8)

[a] PCV13, 13-valent pneumococcal conjugate vaccine; TIV, trivalent inactivated influenza vaccine.

were compared between group 1 and group 2 at 1 month after PCV13. Corresponding two-sided 95% CIs for the GMCs were constructed by back-transformation of the 95% CI for the mean of logarithmically transformed assay results computed using the Student t distribution. For the GMC ratio, the 95% CI was computed using the Student t distribution for the mean difference of the measures on the log scale. Noninferiority was declared if the lower limit of the two-sided 95% CI for the GMC ratio (group 1/group 2) calculated 1 month after PCV13 vaccination was >0.5 (2-fold criterion). This value was selected based on results from several infant PCV7 or 9-valent PCV efficacy trials (24). Therefore, geometric mean immune response values that are within a 2- to 3-fold range are unlikely to manifest as a clinically significant change in the effectiveness of the vaccine. This noninferiority margin was consistent with those in relevant publications at the time of study design (10).

OPA analyses were not prospectively defined, and criteria applied in the IgG analysis in this study and those applied in other pivotal PCV13 studies were applied to the OPA analyses; OPA GMTs were compared between group 1 and group 2 at 1 month after PCV13, and noninferiority was declared if the lower limit of the two-sided 95% CI for the GMT ratio (group 1/group 2) 1 month after PCV13 vaccination was >0.5 (2-fold criterion). A noninferiority margin of −10% was used for the comparison of the percentages of subjects achieving OPA titers of ≥LLOQ.

The fold rises in antibody concentrations and titers for group 1 and group 2 from prevaccination to 1 month postvaccination were summarized by GMC/GMT and CIs and computed using the logarithmically transformed assay results.

The safety comparisons between groups were based on 95% CIs and P values. For local reactions and systemic events, methodology proposed by Chan and Zhang (5) was used to generate exact two-sided CIs and corresponding P values. Comparison of adverse events between groups was conducted using methodology by Miettinen and Nurminen (14).

RESULTS

Baseline characteristics and disposition of participants. A total of 1,158 participants consented, of whom 1,116 were randomized in a 1:1 ratio to receive either PCV13 coadministered with TIV followed 1 month later by placebo (group 1, n = 554) or placebo coadministered with TIV followed 1 month later by PCV13 (group 2, n = 562). Forty-three participants were screened but not randomized. The disposition of participants is shown in Fig. 1. The safety population included any patient who received ≥1 dose of the study vaccine, and it comprised 1,111 participants (n = 551 and 560 in groups 1 and 2, respectively) (Table 1). The evaluable immunogenicity population included 1,063 participants (n = 531 and 532 in groups 1 and 2, respectively), and the baseline characteristics of this population were similar to those of the safety population.

Immunogenicity. (i) Response to TIV. The proportions of participants that achieved a ≥4-fold increase in HAI assay titer for each influenza virus subtype were similar in group 1 and group 2 (A/H1N1, 84.0% and 81.2%, respectively; A/H3N2, 71.1% and 69.5%, respectively; and B, 60.6% and 60.3%, respectively). Noninferiority was met for all three antigens in the influenza vaccine (Table 2).

At baseline, the HAI assay GMTs were similar for groups 1 and 2, and they rose substantially after vaccination. It was noted that baseline HAI assay GMTs for A/H3N2 were higher than those for A/H1N1 and B (Table 3).

(ii) Response to PCV13. IgG antibodies against *S. pneumoniae* serotypes were assessed in a subpopulation of participants in both groups. Before vaccination with PCV13 plus TIV in group 1, baseline IgG GMCs ranged from 0.22 μg/ml (serotype 4) to 2.95 μg/ml (serotype 19A) (data not shown); 1 month after vaccination, the IgG GMCs ranged from 1.15 μg/ml (serotype 3) to 16.70 μg/ml (serotype 19A) (Table 4). Baseline prevaccination IgG GMCs in group 2 (TIV plus placebo; PCV13) ranged from 0.24 μg/ml (serotype 4) to 2.95 μg/ml (serotype 19A) (data not shown). One month after vaccination with PCV13 at dose 2 in group 2, IgG GMCs ranged from 1.45 μg/ml (serotype 3) to 18.84 μg/ml (serotype 19A) (Table 4).

The noninferiority criterion for IgG GMC ratios was met for all pneumococcal serotypes (Table 4). However, 1 month after vaccination with PCV13, point estimate IgG GMCs were lower in group 1 (range, 1.15 to 16.80) than group 2 (range, 1.46 to 18.84)

TABLE 2 Comparison of participants with a ≥4-fold increase in titer for TIV antigens after dose 1 in the evaluable immunogenicity population[a]

TIV	≥4-fold increase in titer				
	Group 1 (PCV13 plus TIV) (n = 530)		Group 2 (placebo plus TIV) (n = 531)		% difference between groups (95% CI)
	n (%)	95% CI	n (%)	95% CI	
A/H1N1	445 (84.0)	80.6, 87.0	431 (81.2)	77.6, 84.4	2.8 (−1.8, 7.4)
A/H3N2	377 (71.1)	67.1, 75.0	369 (69.5)	65.4, 73.4	1.6 (−3.9, 7.2)
B	321 (60.6)	56.3, 64.8	320 (60.3)	56.0, 64.5	0.3 (−5.6, 6.2)

[a] The evaluable population included participants who received both doses of vaccine, provided blood samples within the protocol-defined time limits, and had not had any major protocol violations. CI, confidence interval; PCV13, 13-valent pneumococcal conjugate vaccine; TIV, trivalent inactivated influenza vaccine.

TABLE 3 Standard HAI assay GMTs before and after dose 1 and GMFR after dose 1 in the evaluable immunogenicity population[a]

TIV antigen vaccine received	GMT (95% CI)		Fold rise after dose 1/before dose 1 GMFR (95% CI)
	Before dose 1	After dose 1	
A/H1N1			
Group 1 (PCV13 plus TIV) ($n = 530$)	26.0 (23.3, 29.1)	331.8 (300.6, 366.2)	12.8 (11.3, 14.4)
Group 2 (placebo plus TIV) ($n = 531$)	24.4 (21.9, 27.2)	330.6 (298.3, 366.4)	13.6 (11.9, 15.4)
A/H3N2			
Group 1 (PCV13 plus TIV) ($n = 530$)	43.4 (37.9, 49.8)	443.2 (399.8, 491.2)	10.2 (8.9, 11.7)
Group 2 (placebo plus TIV) ($n = 531$)	49.5 (43.1, 56.8)	477.7 (427.4, 533.9)	9.7 (8.4, 11.2)
B			
Group 1 (PCV13 plus TIV) ($n = 530$)	14.0 (12.9, 15.2)	67.7 (60.7, 75.5)	4.8 (4.4, 5.4)
Group 2 (placebo plus TIV) ($n = 531$)	14.9 (13.6, 16.2)	77.8 (70.0, 86.6)	5.2 (4.7, 5.9)

[a] The evaluable population included participants who received both doses of vaccine, provided blood samples within the protocol-defined time limits, and had not had any major protocol violations. CI, confidence interval; GMFR, geometric mean fold rise; GMT, geometric mean titer; *n*, number of participants with valid and determinate assay results at the given visit; HAI, hemagglutination inhibition; PCV13, 13-valent pneumococcal conjugate vaccine; TIV, trivalent inactivated influenza vaccine.

and were significantly lower for serotypes 1, 3, 4, 6B, 7F, 9V, 14, and 18C when PCV13 was given concomitantly with TIV than when PCV13 was given 1 month later.

The OPA titers were assayed *post hoc* in a subpopulation of participants in both groups. Before vaccination with PCV13 plus TIV in group 1, baseline OPA GMTs ranged from 5 (serotype 5) to 82 (serotype 14) (data not shown); 1 month after vaccination, the OPA GMTs ranged from 61 (serotype 3) to 2,226 (serotype 6B) (Table 5). In group 2, baseline OPA GMTs ranged from 5 (serotype 5) to 67 (serotype 14) (data not shown); 1 month after vaccination with PCV13 at dose 2, the OPA GMTs ranged from 76 (serotype 3) to 3,246 (serotype 6A) (Table 5).

The noninferiority criterion for comparison of OPA GMTs was met for 8 of 13 pneumococcal serotypes (serotypes 3, 4, 6A, 6B, 14, 18C, 19A, and 23F) (Table 5). However, OPA GMTs were significantly lower (the upper limit of the 95% CI for the geometric mean ratio [GMR] was <1) in group 1 than in group 2 for all serotypes except 6B, 18C, and 23F.

In the *post hoc* analysis, ≥74% of a subpopulation of participants in both groups achieved pneumococcal OPA antibody titers of ≥LLOQ for the 13 serotypes 1 month after receiving PCV13 (Table 6). Although the noninferiority margin (lower limit of the 95% CI for the difference >−10%) was achieved for 12 of the 13 serotypes, the percentage of participants achieving titers of

TABLE 4 Comparison of pneumococcal IgG GMCs 1 month after a dose of PCV13 in the evaluable immunogenicity population[a]

Serotype	Group 1 (PCV13 plus TIV; placebo) after dose 1		Group 2 (placebo plus TIV; PCV13) after dose 2		Vaccine comparison ratio (95% CI)
	n	GMC (μg/ml)	*n*	GMC (μg/ml)	
1	292	4.05	289	5.45	0.74 (0.58, 0.95)[b]
3	290	1.15	288	1.46	0.79 (0.66, 0.93)[b]
4	290	2.35	288	3.41	0.69 (0.55, 0.87)[b]
5	293	6.03	289	7.18	0.84 (0.67, 1.05)
6A	293	5.78	288	6.70	0.86 (0.70, 1.06)
6B	292	7.58	289	10.09	0.75 (0.60, 0.93)[b]
7F	293	8.14	289	10.57	0.77 (0.63, 0.95)[b]
9V	293	4.96	289	6.97	0.71 (0.59, 0.86)[b]
14	294	10.77	288	14.05	0.77 (0.60, 0.98)[b]
18C	293	9.65	288	13.49	0.72 (0.58, 0.88)[b]
19A	294	16.80	289	18.84	0.89 (0.74, 1.08)
19F	291	6.13	286	7.13	0.86 (0.67, 1.10)
23F	294	7.17	289	8.54	0.84 (0.66, 1.08)

[a] The evaluable population included participants who received both doses of vaccine, provided blood samples within the protocol-defined time limits, and had not had any major protocol violations. CI, confidence interval; GMC, geometric mean concentration; *n*, number of participants with valid and determinate assay results at the given visit; PCV13, 13-valent pneumococcal conjugate vaccine; TIV, trivalent inactivated influenza vaccine.
[b] Statistically significant lower response in group 1 relative to group 2 based on the upper limit of the 95% CI being <1.0.

TABLE 5 Comparisons of pneumococcal opsonophagocytic activity GMTs 1 month after a dose of PCV13 in the evaluable immunogenicity population[a]

Serotype	Group 1 (PCV13 plus TIV; placebo) after dose 1		Group 2 (placebo plus TIV; PCV13) after dose 2		Vaccine comparison ratio (95% CI)
	n	GMT	*n*	GMT	
1	289	150	285	264	0.6 (0.43, 0.75)[b,c]
3	280	61	274	78	0.8 (0.63, 0.98)[b]
4	280	1,657	282	2,203	0.8 (0.60, 0.95)[b]
5	273	100	281	204	0.5 (0.35, 0.69)[b,c]
6A	283	2,160	289	3,157	0.7 (0.51, 0.91)[b]
6B	279	2,421	286	3,215	0.8 (0.57, 1.00)
7F	268	1,584	281	2,691	0.6 (0.43, 0.80)[b,c]
9V	285	1,053	285	1,749	0.6 (0.43, 0.85)[b,c]
14	284	1,020	283	1,554	0.7 (0.51, 0.85)[b]
18C	279	1,440	285	1,978	0.7 (0.53, 1.00)
19A	281	777	277	1,022	0.8 (0.61, 0.95)[b]
19F	283	379	283	625	0.6 (0.43, 0.85)[b,c]
23F	271	382	281	483	0.8 (0.54, 1.16)

[a] The evaluable population included participants who received both doses of vaccine, provided blood samples within the protocol-defined time limits, and had not had any major protocol violations. GMTs, geometric mean titers; CI, confidence interval; *n*, number of participants with valid and determinate assay results at the given visit; PCV13, 13-valent pneumococcal conjugate vaccine; TIV, trivalent inactivated influenza vaccine.
[b] Statistically significant lower response in group 1 relative to group 2 based on the upper limit of the 95% CI being <1.0.
[c] Noninferiority criterion not met for the serotype (i.e., the lower limit of the 95% CI was <0.5).

TABLE 6 Comparison of participants achieving a pneumococcal opsonophagocytic activity antibody titer greater than the LLOQ 1 month after a dose of PCV13 in the evaluable immunogenicity population[a]

	Group 1 (PCV13 plus TIV)			Group 2 (PCV13)			
Serotype	*N*	*n* (%)	95% CI	*N*	*n* (%)	95% CI	% difference (95% CI)
1	289	257 (88.9)	84.7, 92.3	285	268 (94)	90.6, 96.5	−5.1 (−9.9, −0.4)
3	280	247 (88.2)	83.8, 91.7	274	250 (91.2)	87.2, 94.3	−3.0 (−8.2, 2.1)
4	280	273 (97.5)	94.9, 99.0	282	277 (98.2)	95.9, 99.4	−0.7 (−3.5, 1.9)
5	273	202 (74.0)	68.4, 79.1	281	244 (86.8)	82.3, 90.6	−12.8 (−19.4, −6.2)
6A	283	272 (96.1)	93.2, 98.0	289	280 (96.9)	94.2, 98.6	−0.8 (−4.1, 2.4)
6B	279	269 (96.4)	93.5, 98.3	286	276 (96.5)	93.7, 98.3	−0.1 (−3.4, 3.2)
7F	268	248 (92.5)	88.7, 95.4	281	270 (96.1)	93.1, 98.0	−3.5 (−7.7, 0.4)
9V	285	252 (88.4)	84.1, 91.9	285	264 (92.6)	89.0, 95.4	−4.2 (−9.2, 0.6)
14	284	273 (96.1)	93.2, 98.1	283	275 (97.2)	94.5, 98.8	−1.0 (−4.3, 2.1)
18C	279	261 (93.5)	90.0, 96.1	285	270 (94.7)	91.5, 97.0	−1.2 (−5.3, 2.8)
19A	281	276 (98.2)	95.9, 99.4	277	273 (98.6)	96.3, 99.6	−0.3 (−2.8, 2.1)
19F	283	249 (88.0)	83.6, 91.5	283	259 (91.5)	87.6, 94.5	−3.5 (−8.7, 1.5)
23F	271	229 (84.5)	79.6, 88.6	281	242 (86.1)	81.5, 89.9	−1.6 (−7.6, 4.3)

[a] The following cutoffs (lower limits of quantitation [LLOQs]) were used for the mcOPA assays: serotype 1, 1:18; serotype 3, 1:12; serotype 4, 1:21; serotype 5, 1:29; serotype 6A, 1:37; serotype 6B, 1:43; serotype 7F, 1:210; serotype 9V, 1:345; serotype l4, 1:35; serotype 18C, 1:31; serotype 19A, 1:18; serotype 19F, 1:48; and serotype 23F, 1:13. The evaluable population included participants who received both doses of vaccine, provided blood samples within the protocol-defined time limits, and had not had any major protocol violations. CI, confidence interval; *N*, number of participants with determinate postvaccination OPA antibody titers to the given serotype; *n*, number of participants with OPA titers ≥LLOQ for the given serotype; PCV13, 13-valent pneumococcal conjugate vaccine; TIV, trivalent inactivated influenza vaccine.

≥LLOQ was higher for all serotypes in group 2, where PCV13 was administered 1 month after TIV, than in group 1. Significant differences were observed for serotypes 1 and 5.

Safety. After receipt of PCV13, local reactions at the pneumococcal injection site were similar in groups 1 (postdose 1) and 2 (postdose 2) (88.6% versus 85.1%, respectively), and the majority were mild (Table 7). Pain and limitation of arm movement were reported more frequently than redness and swelling. Systemic

TABLE 7 Percentage of participants with local reactions at the PCV13 injection site or systemic events within 14 days of vaccination: safety population[a]

				Group 1, dose 1, vs group 2, dose 1[b]		Group 1, dose 1, vs group 2, dose 2[b]	
Reaction or event	Group 1, dose 1 (PCV13 plus TIV), % (*n*/*N*)	Group 2, dose 1 (placebo plus TIV), % (*n*/*N*)	Group 2, dose 2 (PCV13), % (*n*/*N*)	Difference, % (95% CI)	*P* value	Difference, % (95% CI)	*P* value
Local reactions							
Any	88.6 (420/474)	39.4 (128/325)	85.1 (388/456)	49.2 (43.0, 55.2)	<0.001	3.5 (−0.8, 7.9)	0.11
Redness	16.3 (46/282)	3.0 (8/263)	12.1 (31/257)	13.3 (8.5, 18.4)	<0.001	4.2 (−1.7, 10.3)	0.16
Swelling	18.4 (53/288)	3.0 (8/263)	14.7 (39/265)	15.4 (10.4, 20.6)	<0.001	3.7 (−2.6, 10.0)	0.25
Pain	86.8 (407/469)	37.1 (119/321)	84.5 (383/453)	49.7 (43.4, 55.7)	<0.001	2.2 (−2.3, 6.8)	0.34
Limitation of arm movement	35.6 (113/317)	8.9 (24/270)	42.5 (135/318)	26.8 (20.3, 33.0)	<0.001	−6.8 (−14.4, 0.8)	0.08
Systemic events							
Any	86.2 (417/484)	75.8 (326/430)	76.7 (326/425)	10.3 (5.2, 15.5)	<0.001	9.5 (4.3, 14.6)	<0.001
Fever ≥38°C but <38.5°C	1.5 (4/261)	1.2 (3/259)	1.2 (3/241)	0.4 (−2.0, 2.9)	0.80	0.3 (−2.2, 2.8)	0.86
Fever ≥38.5°C but <39°C	1.5 (4/262)	0 (0/257)	0.8 (2/240)	1.5 (0.0, 3.9)	0.05	0.7 (−1.6, 3.1)	0.57
Fever ≥39°C but ≤40°C	0.4 (1/261)	0 (0/257)	0.4 (1/240)	0.4 (−1.1, 2.1)	0.51	0.0 (−1.9, 1.7)	>0.99
Fever >40°C	0 (0/261)	0.4 (1/257)	0 (0/240)	−0.4 (−2.2, 1.1)	0.52	0.0 (−1.6, 1.4)	>0.99
Fatigue	58.1 (226/389)	52.4 (188/359)	51.8 (175/338)	5.7 (−1.4, 12.8)	0.12	6.3 (−0.9, 13.6)	0.09
Headache	65.9 (263/399)	56.5 (216/382)	50.9 (172/338)	9.4 (2.5, 16.2)	<0.01	15.0 (7.9, 22.1)	<0.001
Chills	31.4 (96/306)	21.0 (61/291)	24.6 (68/276)	10.4 (3.4, 17.4)	<0.01	6.7 (−0.6, 14.0)	0.07
Rash	12.6 (35/278)	4.9 (13/264)	9.5 (24/252)	7.7 (2.5, 12.6)	<0.01	3.1 (−2.4, 8.5)	0.27
Vomiting	5.3 (14/266)	3.4 (9/262)	6.1 (15/247)	1.8 (−1.8, 5.6)	0.32	−0.8 (−5.1, 3.3)	0.78
Decreased appetite	30.2 (95/315)	22.6 (68/301)	25.8 (72/279)	7.6 (0.6, 14.5)	0.03	4.4 (−2.9, 11.6)	0.24
New muscle pain	65.5 (252/385)	37.7 (123/326)	59.1 (207/350)	27.7 (20.5, 34.7)	<0.001	6.3 (−0.8, 13.3)	0.08
Any aggravated muscle pain	34.7 (109/314)	24.1 (71/294)	36.7 (112/305)	10.6 (3.3, 17.8)	<0.01	−2.0 (−9.6, 5.6)	0.62
New joint pain	33.0 (102/309)	24.7 (73/296)	27.4 (78/285)	8.3 (1.1, 15.6)	0.02	5.6 (−1.8, 13.1)	0.14
Any aggravated joint pain	21.2 (62/292)	18.0 (51/284)	23.8 (67/282)	3.3 (−3.3, 9.8)	0.33	−2.5 (−9.4, 4.4)	0.50

[a] The safety population included all participants who received at least one dose of the study vaccine. CI, confidence interval; PCV13, 13-valent pneumococcal conjugate vaccine; TIV, trivalent inactivated influenza vaccine.

[b] Differences in proportions for local and systemic reactions were expressed as percentages along with exact 2-sided CIs and corresponding *P* values (based on the methodology by Chan and Zhang [5]) for the difference in proportions, group 1 (PCV13 plus TIV then placebo) − group 2 (placebo plus TIV then PCV13), expressed as a percentage.

events after PCV13 were reported more frequently in group 1 (postdose 1) than in group 2 (postdose 2) (86.2% versus 76.7%; $P < 0.001$; Table 6). The most frequently reported events after receipt of PCV13 in group 1 versus group 2 were headache (65.9% versus 50.9%, respectively; $P < 0.001$), new muscle pain (65.5% versus 59.1%, respectively; $P = 0.08$), fatigue (58.1% versus 51.8%, respectively; $P = 0.09$), and any aggravated muscle pain (34.7% versus 36.7%, respectively; $P = 0.62$).

Overall, fever rates were low after any dose in either group, and if fever did occur, it was mild or moderate in severity (Table 7). There were no vaccine-related serious adverse events in the study. Adverse events were reported in 16.7% and 13.9% of participants after dose 1 and 11.7% and 11.8% of participants after dose 2 in groups 1 and 2, respectively. After dose 1, adverse events occurring in ≥2% of the study population in group 1 (PCV13 plus TIV) versus group 2 (placebo plus TIV) included general disorders and administration site conditions (2.5% versus 2.3%, respectively; $P = 0.81$), respiratory, thoracic, and mediastinal disorders (2.0% versus 3.4%, respectively; $P = 0.15$), infections and infestations (6.5% versus 4.6%, respectively; $P = 0.17$), and musculoskeletal and connective tissue disorders (2.7% versus 0.9%, respectively; $P = 0.02$). After dose 2, infections and infestations (4.3% versus 4.1%, respectively; $P = 0.85$) and respiratory, thoracic, and mediastinal disorders (2.0% versus 1.8%, respectively; $P = 0.81$) were the only adverse events occurring in ≥2% of the study population in group 1 (placebo) versus group 2 (PCV13).

DISCUSSION

An increased incidence of IPD has been linked to influenza infection (3, 15). Walter et al. recently examined the burden of invasive pneumococcal pneumonia during a nonpandemic influenza period in the United States (28). The influenza virus was associated with 11 to 14% of pneumococcal pneumonia cases during influenza peaks, showing the advantage of simultaneously preventing pneumococcal infections and influenza. A retrospective study of 98 Japanese adults with chronic respiratory disease suggested that coadministration of pneumococcal and influenza vaccines resulted in significant decreases in the number of respiratory infections along with the number of hospitalizations compared with results for people who received only the influenza vaccine (25).

A large prospective study in Sweden also supports the efficacy of coadministration of pneumococcal and influenza vaccines (6). In this study, 100,242 participants aged ≥65 years were offered one or both vaccines, with 76% choosing to receive both the pneumococcal and influenza vaccines. Over the observation period, rates of hospitalization for both influenza and pneumococcal disease declined in the vaccinated cohort compared with 159,385 comparably aged people who elected not to be vaccinated, and mortality was 57% lower in the vaccinated group. Finally, a study of elderly adults in Italy simultaneously administered influenza and pneumococcal vaccines had a brisk antibody response to both vaccines (9).

The ability to administer PCV13 at an annual visit for influenza vaccination is desirable from both a convenience and a public health perspective to encourage compliance. The present study is the first report of the concomitant administration of a PCV and an influenza vaccine in adults 50 to 59 years of age in the United States. Immunogenicity results show that immune responses for TIV antigens after the concomitant administration of PCV13 and TIV to healthy adults aged 50 to 59 years are robust and noninferior to immune responses after TIV given separately. However, the antipneumococcal IgG responses were lower for all serotypes and statistically significantly lower for 8 of 13 serotypes after concomitant administration of PCV13 and TIV compared with administration of PCV13 alone.

Antipneumococcal OPA assays showed a similar pattern, with significantly lower responses after concomitant administration of PCV13 and TIV than with PCV13 for 10 of 13 serotypes. Although there is no correlate of protection for the LLOQ defined in adults, the proportion of subjects achieving an OPA titer of ≥LLOQ after concomitant PCV13 and TIV was similar to or lower than that with PCV13 given alone, with two serotypes being statistically significantly lower after concomitant PCV13 and TIV. Lower IgG responses after concomitant PCV13 and TIV were also reported in a similarly designed study in Germany in adults of ≥65 years of age (20).

Local reactions associated with the concomitant administration of PCV13 and TIV were comparable to those associated with PCV13 given a month after TIV. More systemic adverse events were seen with the concomitant administration of PCV13 and TIV than with the single administration of either vaccine. Given that two vaccines were administered concomitantly, the higher rate of systemic events does not appear to be unusual and is not considered clinically meaningful. Several local site reactions and systemic events were also reported in group 2 (TIV plus placebo).

This study has some limitations. First, a comparator group receiving PPV23 with TIV was not included. Second, there is no historical control because although PPV23 is approved for adults 50 to 59 years of age, it is not recommended routinely for healthy adults until they reach 65 years of age (1). Finally, the current study evaluated only one formulation of the trivalent influenza vaccine designed for a specific influenza season, and the OPA analyses were performed *post hoc*.

Overall, the concomitant administration of PCV13 and TIV was demonstrated to be immunogenic and well tolerated. Although IgG and OPA responses were lower when comparing concomitant administration of PCV13 and TIV to separate administration of PCV13, it is likely that PCV13 establishes immunologic memory, a common characteristic of conjugated polysaccharide vaccines that is not seen with purified polysaccharide vaccines. In the absence of an established correlate of protection in adults, the clinical significance of the lower antipneumococcal responses seen in group 1 compared with those in group 2 is uncertain. Although the responses seen in the recipients in group 1 were lower than those in group 2, the immune responses to the pneumococcal serotypes when both vaccines were given together met the noninferiority criterion. Particularly in clinical settings where there is an opportunity to immunize against both pneumococcal disease and influenza, concomitant vaccination with PCV13 and influenza vaccine may be considered.

This study also includes a 5-year follow-up, with another dose of PCV13 to be administered 5 years after the first dose, to further assess revaccination responses; follow-up results will be reported at a later date.

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